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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,228	06/05/2001	De Chao Yu	CELL119.3US	8799

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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/875,228	YU ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-13,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-13,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 6/3/04.

Claims 7, 14, 54, 69, 71, 73, and 75 were cancelled as requested.

Claims 1-6, 8-13, 31, and 32 remain pending and are under consideration in this Office Action.

Drawings

Applicant has submitted drawings which are adequate for the purpose of examination.

Rejections Withdrawn

The rejection of claims 1-6, 31, and 32 under 35 USC 112, first paragraph for lack of adequate written description is withdrawn in view of Applicant's amendments requiring that the recited enhancer activity must be contained within a structurally limited 150 base sequence.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 8-13, 31, and 32 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 and 24-31 of US Patent 6,676,935, or claims 1-17 of US Patent No. 6,432,700, or claims 1-8 and 11-15 of US Patent 6,495,130. Although the conflicting claims are not identical, they are not patentably distinct from each other.

US Patent 6,676,935 claims adenoviral vectors comprising an adenoviral gene required for adenoviral replication such as E1A or E1B, wherein the gene is operably linked to a TRE. The specification teaches that a TRE may be an hKLK2-TRE, such as that in SEQ ID NO:3 of '935. See paragraphs 13, and 77, and Fig. 14. It would have been obvious to one of ordinary skill in the art at the time of the invention to use the hKLK2-TRE of '935 because the claims of '935 suggest the use of a TRE, and the specification exemplifies the hKLK2-TRE. Thus the invention as a whole was prima facie obvious.

US Patent 6,432,700 claims adenoviral vectors comprising an adenoviral gene required for adenoviral replication such as E1A or E1B, wherein the gene is operably linked to a TRE. The specification teaches that a TRE may be an hKLK2-TRE, such as that in SEQ ID NO:3 of '700. See paragraphs 4,5, and 80. It would have been obvious to one of ordinary skill in the art at the time of the invention to use the hKLK2-TRE of '700because the claims of '700 suggest the

use of a TRE, and the specification exemplifies the hKLK2-TRE. Thus the invention as a whole was prima facie obvious.

US Patent 6,495,130 claims adenoviral vectors comprising an adenoviral gene required for adenoviral replication such as E1A or E1B, wherein the gene is operably linked to a TRE. The specification teaches that a TRE may be an hKLK2-TRE, such as that in SEQ ID NO:11 of '130. See paragraphs 22, 83, 93 and 95. SEQ ID NO:11 of '130 is identical to instant SEQ ID NO:1. It would have been obvious to one of ordinary skill in the art to use the hKLK2-TRE of '130 because the claims of '130 suggest the use of a TRE, and the specification exemplifies the hKLK2-TRE. Thus the invention as a whole was prima facie obvious.

Claims 1-6, 8-13, 31 and 32 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,585,968, or claims 1-20 and 22-26 of US Patent 6,436,394, or claims 1-26 and 28-54 of US Patent 6,197,293, in view of any one of US Patents 6,676,935, or 6,432,700, or 6,495,130.

US Patent 6,585,968 claims adenoviral vectors comprising an hKLK2-TRE operably linked to an adenoviral gene required for replication, see e.g. claim 22.

US Patent 6,436,394 claims adenoviral vectors comprising an hKLK2-TRE operably linked to an adenoviral gene required for replication, see e.g. claim 13.

US Patent 6,197,293 claims adenoviral vectors comprising adenoviral genes required for replication, wherein the genes are under control of TREs.

The specification teaches that the TRE may be an hKLK2-TRE. See paragraph 16.

None of these patents teaches instant SEQ ID NO:1.

U.S. Patents 6,676,935 (claims 1-21 and 24-31), 6,432,700 (claims1-17), and 6,495,130 (claims 18- and 1-15), are drawn to adenoviral vectors comprising a TRE directing transcription of an adenoviral gene required for replication, such as E1A or E1B. The specifications ofthese patents teach that the TRE may be an hKLK2-TRE, and may be SEQ ID NOS: 3, 3, and 11, respectively, each of which is identical to instant SEQ ID NO:1. It would have been obvious to one of ordinary skill in the art to use in the inventions of the '968, '394, or '293 patents the hKLK2-TRE disclosed in U.S. Patents 6,676,935, or 6,432,700, or 6,495,130, because one could reasonably expect this hKLK2-TRE to function in an adenoviral vector in view of the teachings of these patents, each of which suggests the use of this sequence in an adenoviral vector, operably linked to a gene required for viral replication.

Claims 1-6 and 8-13 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,051,417, in view of any one of US Patents 6,676,935, or 6,432,700, or 6,495,130.

US Patent 6,051,417 claims methods of screening for compounds which alter expression of a prostate-specific enhancer from a human glandular kallikrein (hKLK2) gene, said method employing cells containing an expression

construct, said expression construct comprising a transcriptional initiation region of a prostate specific enhancer from a human glandular kallikrein (hKLK2) gene and a promoter and a marker gene whose expression product provides a detectable signal, wherein said marker gene is under the transcriptional control of said transcriptional initiation region

US Patent 6,051,417 does not teach instant SEQ ID NO:1.

U.S. Patents 6,676,935 (claims 1-21 and 24-31), 6,432,700 (claims1-17), and 6,495,130 (claims 18- and 1-15), are drawn to adenoviral vectors comprising a TRE directing transcription of an adenoviral gene required for replication, such as E1A or E1B. The specifications ofthese patents teach that the TRE may be an hKLK2-TRE, and may be SEQ ID NOS: 3, 3, and 11, respectively, each of which is identical to instant SEQ ID NO:1. It would have been obvious to one of ordinary skill in the art to modify the invention of 6,051,417 by using the hKLK2-TRE disclosed in U.S. Patents 6,676,935, or 6,432,700, or 6,495,130, because one could reasonably expect this hKLK2-TRE to function in the method of 6,051,417 in view of the teachings of these patents.

Claims 1-6, 8-14, 31, and 32 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of copending published US Application 20030152553 , or claims 1-9, 19, 22, 26-39, 41, 49-55, 59-63, 67, and 68 of copending published US Application 20030118555, or claims 1-12, 14, 18-28, 41-43, and 47-58 of copending published US Application 20030068307.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Each of the cited Applications claims adenoviral vectors comprising an hKLK2-TRE operably linked to a gene required for viral replication. Each of the Applications discloses instant SEQ ID NO:1 as an example of an hKLK2-TRE, therefore it would have been obvious to use instant SEQ ID NO: 1 as an hKLK2-TRE in the inventions of each of these Applications.

Response to Arguments

Applicant's arguments filed 6/3/04 have been fully considered but they are not persuasive. With regard to each rejection Applicant states that the instant claims are not obvious over the cited art. These statements are unpersuasive because they are only statements of opinion and are not supported by evidence or reason. At page 5 of the response Applicant indicates that filing of a terminal disclaimer will be considered upon indication of otherwise allowable subject matter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claim 1-6 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 are drawn to the genus of isolated polynucleotides comprising 150 contiguous nucleotides of nucleotides 1-11047 of SEQ ID NO:1, wherein the 150 contiguous nucleotides have prostate-specific enhancer activity, and are not found in SEQ ID NO:2 or SEQ ID NO:3. Claim 6 is drawn to a broader genus of isolated polynucleotides comprising 150 contiguous nucleotides having as little as 90% identity to a sequence within of nucleotides 1-11047 of SEQ ID NO:1, wherein the 150 contiguous nucleotides have prostate-specific enhancer activity, and are not found in SEQ ID NO:2 or SEQ ID NO:3.

A review of the specification shows that Applicant considers the invention to be a prostate-specific enhancer located within SEQ ID NO:1 that is active in prostate cells bearing androgen receptors. SEQ ID NO:1 contains an enhancer which is active in prostate cells expressing androgen receptors (LNCaP), but inactive in prostate cells lacking androgen receptors (PC-3). Ectopic expression of androgen receptors in PC-3 cells was not sufficient to provide androgen-sensitive enhancer activity in PC-3 cells, indicating that LNCaP cells have some unknown factor that is required for activity of the SEQ ID NO:1 enhancer. See paragraph 367.

The specification discloses a single species of the claimed invention, and several active fragments of that species. Deletion analysis of SEQ ID NO:1 defines a core enhancer of 1172 bases from position 7200-8371 that has full enhancer activity (about 90-fold induction in LNCaP cells when linked to a minimal promoter). A minimal fragment from position 8021-8371 has reduced activity, (37-fold induction). A fragment from position 8128-8263 did not show any enhancer activity. See pages 101 and 102, and Figs. 24A and 24B. The specification discloses an androgen response element at position 8192-8206 of SEQ ID NO:1 that is necessary but not sufficient for enhancer function. Two different mutated versions of this ARE eliminate enhancer activity when either is inserted in normal context within nucleotides 7200-8371 (the maximally active core enhancer fragment of SEQ ID NO:1). This ARE is located within the inactive 8128-8263 fragment, so it is necessary but not sufficient for activity. See page 103, line 4 to page 104, line 6, and Fig. 11. So it appears that the minimal fragment disclosed which is sufficient for prostate-specific enhancer activity is the fragment comprising bases 8021-8371, and that an ARE at bases 8192-8206, and unknown sequences in bases 8021-8127 and/or 8264-8371, are required for activity. The specification does not disclose any species of the claimed genus that lacks bases 8021-8371. It follows that no species of the genus of prostate specific enhancers from 150-350 nucleotides in length is disclosed.

Bases 1-11047 of SEQ ID NO:1 comprise over 10,000 150 base fragments that do not comprise bases 8021-8371. It is possible that some of these sequences comprise prostate specific enhancers. However, the

specification fails to provide any description of the structural characteristics that are necessary to provide the claimed function, e.g. transcription factor binding sites, and fails to disclose any species of the claimed genus that lacks bases 8021-8371, i.e. any species that is less than 351 bases in length. Thus one of skill in the art could not conclude that Applicant was in possession of any fragment of SEQ ID NO:1 that has prostate specific enhancer activity, but lacks bases 8021-8371 of SEQ ID NO:1.

Enablement

Claims 1-4 and 6 stand rejected under 35 U.S.C. 112, first paragraph. Claims 1-4 and 6 are not adequately enabled because the specification, while being enabling for nucleic acids comprising bases 1-11407 of SEQ ID NO:1, and for fragments of bases 1-11407 of SEQ ID NO:1 that comprise nucleotides 8021-8371 and that comprise prostate-specific enhancer activity, does not reasonably provide enablement for isolated polynucleotides comprising prostate-specific enhancer activity wherein the polynucleotides do not comprise nucleotides 8021-8371 of SEQ ID NO:1.

Claims 1-4 and 6 stand rejected under 35 U.S.C. 112, first paragraph. Claims 1-4 and 6 are not adequately enabled because the specification, while being enabling for nucleic acids that comprise nucleotides 8021-8371, and comprise prostate-specific enhancer activity, does not reasonably provide enablement for isolated polynucleotides comprising prostate-specific enhancer

activity wherein the polynucleotides do not comprise nucleotides 8021-8371 of SEQ ID NO:1.

Claims 1-4 are drawn to isolated polynucleotides containing 150 contiguous nucleic acids from nucleotides 1-11407 of SEQ ID NO:1 that are not present in SEQ ID NOS: 2 or 3, wherein the 150 contiguous nucleotides comprise enhancer activity. Claim 6 is drawn to an isolated polynucleotide that comprises 150 contiguous polynucleotides with at least about 90% identity to any sequence within nucleotides 1-11407 of SEQ ID NO:1. The 150 contiguous nucleotides cannot be a sequence present in SEQ ID NOS: 2 or 3.

Pertinent teachings of the specification are discussed above. In brief, the specification has not disclosed any segment of SEQ ID NO:1 that has prostate-specific enhancer activity and lacks nucleotides 8021-8371, so the specification has not disclosed any example of a 150 base sequence with prostate specific enhancer activity. In contrast, the specification has disclosed a 146 base fragment within bases 8021-8371 that lacks enhancer activity, (i.e. bases 8128-8263). While bases 8021-8371 comprise an androgen response element at bases 8192-8206 that is required for activity, this element is not sufficient for activity, suggesting that unknown sequence elements in bases 8021-8127 and/or 8264-8371 are required for activity. The specification does not disclose the nature of these elements or the transcription factors that are necessary for function of the enhancer. The specification does not provide any guidance as to what sequence modification within the critical region of bases 8021-8127 and/or 8264-8371 are allowed and which will destroy function. The specification

provides no guidance or working example regarding sequences within SEQ ID NO:1 that function as prostate specific enhancers but do not comprise nucleotides 8021-8371, and it is entirely unpredictable what specific sequences are required for enhancer function. Absent any guidance, one of skill in the art is left to trial and error experimentation in order to determine what sequence fragments and variants of SEQ ID NO:1, and what variants of bases 8021-8371 of SEQ ID NO:1, will function as enhancers. One might argue that it would not be undue experimentation to construct and assay individual putative enhancers in order to determine empirically what sequence alterations are allowable. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added.

In this case there are no known scientific laws governing the sequences which are generally useful as prostate-specific enhancers. The prior art and specification combined do not provide the requisite guidance that would allow one of skill in the art to make prostate-specific enhancers, other than those containing at bases 8021-8371 of SEQ ID NO:1, without undue experimentation, i.e. either first discovering what factors are required for activity of the enhancer,

where the binding sites for these factors are, and what sequence alterations in these sites are permitted, or alternatively screening random variants of SEQ ID NO:1 in order to find active enhancers. With regard to claim 6, neither the specification nor the prior art provides guidance as to what modifications to bases 8021-8371 are permissible, and which modifications will inactivate the enhancer contained in this sequence. Due to the unpredictability associated with this process, the lack of guidance and working examples, and the large number of variant sequences that must be screened by trial and error, one would have to perform undue experimentation in order to make the claimed invention.

Response to Arguments

Applicant's arguments filed 6/3/04 have been fully considered but they are not persuasive.

Applicant addresses the written description rejection at page 6 of the rejection, stating that the claims have been amended in accordance with the Examiner's suggestions. A review of the previous Action shows that the Examiner stated that the rejection could be overcome by linking a required function with a required structure, i.e. wherein the required structure has enhancer activity. Applicant's amendment fails to overcome the rejection because the required structure, i.e. bases 8021-8371 of SEQ ID NO:1 was not linked to the recited function.

With regard to the enablement rejection, Applicant argues at pages 6 and 7 of the response that one of skill in the art can readily utilize the specific

polynucleotide sequence of SEQ ID NO:1, in combination with assays and guidance for determination of activity (e.g. in Example 7 which presents a deletion analysis of SEQ ID NO:1), to determine which polynucleotides of at least 150 bp have enhancer activity. This argument is unpersuasive because as noted above, there are in excess of 10,000 150 base fragments of SEQ ID NO:1 that lack bases 8021-8371, but the specification provides no guidance as to which of these fragments should be screened. No guidance is offered regarding selecting a sequence to assay, necessitating trial and error experimentation. Applicant has provided no evidence that a trial and error approach does not represent undue experimentation. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.